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Prospective Assessment of Risks for Cervicomedullary-Junction Compression in Infants with Achondroplasia

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Summary

Achondroplasia, the most common heritable skeletal dysplasia, may result in abnormality at the craniocervical junction, which is a potentially lethal problem in a subset of young infants with this disorder. We evaluated and followed an unbiased and unselected consecutive series of infants with achondroplasia, to better document the occurrence, frequency, and clinical presentation of craniocervical abnormalities. Of 53 prospectively ascertained infants, 5 were judged to have sufficient craniocervical junction compression to require surgical decompression. Intraoperative observation always showed marked abnormality of the cervical spinal cord, and all operated-on children showed marked improvement of neurological function. The most frequent clinical abnormalities within this subset were those expected for high cervical myelopathy. The best predictors of need for suboccipital decompression included lower-limb hyperreflexia or clonus, on examination; central hypopnea demonstrated by polysomnography; and foramen magnum measures below the means for children with achondroplasia. Infants with achondroplasia are at risk for potentially lethal sequelae of craniocervical junction abnormalities; selective intervention can be life and health saving, but individuals at high risk will be identified only if all affected infants undergo comprehensive assessment in infancy.

Introduction

A risk of sudden unexpected death in infants with heterozygous achondroplasia was first documented about a decade ago (Pauli et al. 1984). While uncontrolled and retrospective, that survey demonstrated an excess of deaths in the first year of life, most or all of which were attributable to abnormalities at the craniocervical junction (Pauli et al. 1984). In the past decade, some progress has been made in understanding the source and consequences of this problem in achondroplasia (e.g., see Reid et al. 1987; Wang et al. 1987; Nelson et al. 1988; Thomas et al. 1988; Hecht et al. 1989; Pauli et al. 1992; Francomano et al. 1993). Hecht et al. (1987) showed that the excess risk of death in infants with achondroplasia may approach 7.5%, largely because of cervical cord compression. Since achondroplasia occurs about once in every 25,000 births (Oberklaid et al. 1979), this would imply that each year in the United States ~10 infants with achondroplasia die secondary to craniocervical junction complications. In addition, cervical myelopathic complications may arise at later times in childhood (Yang et al. 1977; Yamada et al. 1981; Blondeau et al. 1983; Colamaria et al. 1991).

Nonspecific interventions, based on a pathoanatomic understanding of the process, may decrease this risk somewhat (Pauli et al. 1984; Reid et al. 1987). Definitive treatment, when indicated, requires neurosurgical suboccipital decompression (Yamada et al. 1981; Reid et al. 1987; Wang et al. 1987; Carson et al. 1988; Colamaria et al. 1991). Given that surgery itself is not without risk (Wassman and Rimoin 1988; Francomano et al. 1993), it is critical to determine if the group of children with achondroplasia who are at high risk for death or neurological and respiratory sequelae can be identified prospectively. Through ongoing evaluation of a group of infants whom we have prospectively assessed and in whom we have virtually complete longitudinal follow-up, we can estimate, within an unbiased population of infants with achondroplasia, the frequency of clinical and laboratory features referable to abnormalities of the craniocervical junction, document the frequency with which suboccipital decompressive surgery was deemed necessary, and identify the best predictors of the need for decompressive surgery.

Subjects and Methods

Subjects Assessed

In the past 12 years a total of 75 infants and young children with achondroplasia, primarily from Wisconsin, Illinois, Michigan, Minnesota, and Iowa, were assessed through the Midwest Regional Bone Dysplasia Clinic of the Clinical Genetics Center of the University of Wisconsin. Virtually all were comprehensively evaluated; most were examined by the same pediatric geneticist; and none has been lost to follow-up. Some individuals were referred with specific concerns. Therefore, the total population of 75 was

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divided into two groups—those who were nonselectively and prospectively ascertained (with respect to risks for cervicomedullary junction compression) and the remainder, in whom neurological and/or respiratory concerns precipitated referral. Criteria for inclusion within the prospective group included referral without explicit reference to central respiratory and/or neurological impairment, referral and evaluation prior to 1 year of age, and follow-up at least through 1 year of age at the time of this analysis. Of 75 referred, 53 children met these criteria and constitute the prospective group.

Clinical Assessment

The following information was gathered on prospectively ascertained infants:

- *Medical history* emphasizing respiratory and neurological history, including parental observations or reports of tachypnea, respiratory distress, apnea, color changes, excessive hypotonia, movement asymmetries, seizures, clonus, and disproportionate developmental delay;
- *Physical examination* including documentation of craniofacial characteristics and measurements, neurological evaluation including estimation of severity of truncal and limb hypotonia, head control, asymmetries, abnormalities of strength or resistance, deep-tendon reflexes, presence of clonus, and demonstrable sensory changes;
- *Computed tomography* of the brain and of the craniocervical junction, including bone windows and thin cuts.
- *Polysomnographic evaluation* including, in all instances, an overnight study and, in most cases, monitoring of sleep state, heart rate, oxygen saturation, chest and abdominal impedance, nasal and oral air flow, and end-tidal carbon dioxide levels.

In those with abnormal results from such studies, magnetic resonance imaging of the brainstem and cervical cord was completed.

Early in the course of this series, somatosensory evoked–potential testing was also performed (Nelson et al. 1984). However, these evaluations resulted in a high false-positive rate: of 11 studies completed, results of only 2 were judged to be normal for age, results of 2 were indeterminate, and results of 7 were clearly abnormal; within the latter group, 2 children had other features of craniocervical junction compression, while the remaining 5 were neurologically normal and remained clinically healthy. Given these initial findings, this component of the assessment was discontinued.

Data Analysis

In an effort to identify differences between those who underwent suboccipital decompressive surgery and those who did not, the following analyses were undertaken. A data form was devised that ensured uniform collection of clinical information for all study variables. Variables evaluated included demographic information (sex, race, and age at examinations), perinatal historical information (birth weight, birth length, birth head circumference, gestational age, Apgar scores, and mode of delivery), neurological history in the first year of life (disproportionate developmental delays, observed asymmetries, apparent weakness, severity of hypotonia, opisthotonos or intermittent hypertonicity, observed clonus, seizures, and apparent sensory changes), neurological examination (cranial nerve findings, truncal tone, limb tone, limb resistance, asymmetries, deep-tendon reflexes, and presence of clonus), craniofacial and general clinical examination (head circumference, rate of head growth, fontanel size and character, superficial venous prominence, severity of craniofacial disproportion, parietal bossing, and frontal bossing), computed tomography (ventricular size, amount of extra-axial fluid, and transverse and sagittal foramen magnum measures and equivalent centiles for infants with achondroplasia), polysomnography (apnea index, respiratory-disturbance index, baseline and lowest oxygen saturations, severity of central apnea, and severity of central hypopnea), somatosensory evoked–potential testing (when completed), magnetic resonance imaging (when completed), and documentation of surgical intervention (age of procedure, intraoperative findings, and outcome).

Collected data were entered into a custom-designed WISAR (Wisconsin Information Storage and Retrieval) database and were transferred to SPSS (Statistical Package for Social Sciences, version 4.0/4.1 for VAX) for analysis. Fisher's exact test (one-tailed) was used to identify variables showing significant differences between those who underwent suboccipital decompression and those who did not. Logistic regression was attempted on those factors that seemed to be predictive. Sensitivity, specificity, accuracy, and positive and negative predictive values were computed for those variables that appeared to be predictive for the need for suboccipital decompression, singularly and in groups.

Results

Demographic Characteristics of the Study Population

Features of the 75 infants assessed through the Midwest Regional Bone Dysplasia Clinic are shown in table 1. Both prospective and nonprospective groups had nearly equal numbers of males and females and, reflective of the geographic referral base, were largely Caucasian. Ethnicity of the two groups differs only in that most individuals of Korean origin were nonprospectively ascertained; this reflects the adoption later in infancy of these individuals, which precluded early assessment. There were no differences between prospective and nonprospective groups, with respect to gestation, frequency of prematurity, or of birth weights, birth lengths, and birth head circumferences. A larger proportion of the prospectively assessed group had one or both parents affected with achondroplasia, likely a reflection of their awareness of available medical services.

Table 1

Demographic Characteristics of Infants with Achondroplasia Followed in the Midwest Regional Bone Dysplasia Clinic

Feature	Prospective Group (N = 53)	Nonprospective Group (N = 22)
Sex:		
Male	27 (50.9%)	12 (54.5%)
Female	26 (49.1%)	10 (45.5%)
Race/ethnicity:		
Caucasian	47 (88.7%)	17 (77.3%)
African American	2	0
Hispanic	3	0
Asian Indian	0	1
Korean	1	4
Gestation:		
Mean age (in wk)	38.6	38.6
No. of premature births (<37 wk)	7/49 (14.3%)	3/16 (18.8%)
Birth measures:		
Mean weight (in kg)	3.169	3.227
Mean length (in cm)	46.96	46.63
Mean head circumference (in cm)	36.15	36.66
Parental genotype:		
No. of families with affected parent	11/50 (22.0%)	2/17 (11.8%)
Mother affected (no. of children)	4 (5)	2 (4)
Father affected (no. of children)	5 (7)	0
Both affected (no. of children)	2 (2)	0
Unknown (adoption)	1	3

Two deaths occurred in this 12-year period. One instance is detailed below. The second occurred in a premature male who experienced severe respiratory-distress syndrome, recurrent apnea, and anoxic encephalopathy. He died while in an infant intensive-care unit. It is uncertain whether the neuroanatomic features attributable to achondroplasia contributed to his death.

Characteristics of Individuals Undergoing Suboccipital Decompression

Within the entire population, 10 (13.3%) infants were ultimately judged to be in need of suboccipital decompressive surgery, including 5 (9.4%) of those prospectively ascertained. The age at which decompression occurred was considerably earlier in the prospective group (mean age 10.7 mo; range 8.3–12.8 mo) than in the others (24.0 mo; range 7.6–51.8 mo). In demographic features there were no differences between the decompressed and nondecompressed groups. In particular, there was no correlation between parental genotype and need for decompression: 2 of 10 children in the decompressed group had an affected parent, whereas 16 of 61 in the nondecompressed group had one or both parents affected with achondroplasia (Fisher's exact test, one-tailed, P = .51 [not significant]). Nor was there correlation between need for decompression and method of delivery (4 of 9 in the decompressed group and 26 of 59 in the nondecompressed group were delivered vaginally; Fisher's exact test, one-tailed, P = .62 [not significant]).

In every instance the decision to operate was made only when there were abnormalities by neurological history, by neurological examination, *and* by neuroimaging (table 2). Most features seen in those who underwent craniocervical junction decompression were those that one might anticipate for high cervical myelopathy (table 2). Additional accompaniments of symptomatic cord compression included neck hyperextension (4/10 of those undergoing decompressive surgery), opisthotonic posturing (5/10), failure to thrive (2/10), and apneustic breathing (1/10).

Decompressive surgery was completed, in each instance, by a pediatric neurosurgeon, and, in most cases, within a single center (Children's Memorial Hospital, Chicago). In every instance, obvious abnormality of the upper cervical cord was demonstrated, intraoperatively described as "striking indentation of the spinal cord," "marked cord deformation," "marked compression of the cord," "ribboning of the cord," etc. In two instances, fibrous constriction bands were identified. In one case (nonprospective patient 3 in table 2), this might have resulted in inaccurate estimation of the size of the foramen magnum, since that fibrous region was nonossified. Within the prospectively ascertained group, all children operated on demonstrated (usually dramatic) improvement of neurological function. None has significant neurological sequelae. In contrast, children within the nonprospective group, some of whom were referred be-

Table 2

Features of Infants with Achondroplasia Who Underwent Suboccipital Decompressive Surgery

	Prospective Group					Nonprospective Group					
	1	2	3	4	5	1	2	3	4	5	Total
Neurological history:											
Developmental delays[a]	+		+			+			+	+	5/10
Movement asymmetry		+	+		+	+		+	+	+	7/10
Weakness[b]	+		+			+			+	+	5/10
Apparent sensory changes[c]							+			+	2/10
Arching/opisthotonos				+		+	+	+	+		5/10
Ankle clonus by history		+		+							2/10
Seizures	+							+			2/10
Other		+[d]	+[e]	+[f]		+[g]	+[h]	+[i]	+[j]	+[k]	
Abnormal in any way	+	+	+	+	+	+	+	+	+	+	10/10
Neurological examination:											
Cranial nerve abnormality						+[l]					1/10
Decreased truncal tone[m]			+			+			+	+	4/10
Decreased limb tone[m]	+		+		+	+			+	+	6/10
Decreased limb resistance/strength[m]	+					+			+		3/10
Asymmetric resistance/strength									+		1/10
Hyperreflexia/clonus		+	+	+	+		+		+		6/10
Reflex asymmetry		+	+	+		+			+		5/10
Other	+[n]		+[o]			+[p]	+[n]		+[n]		
Abnormal in some way	+	+	+	+	+	+	+	+	+	+	10/10
Polysomnography:											
Hypopneas with desaturation ≤85%		+	+	+	+	+					5/10
Neuroimaging:											
Foramen:											
Longitudinal measure below mean for achondroplasia	+		+		+				+	+	5/10
Transverse measure below mean for achondroplasia	+	+	+	+	+						5/10
Obliteration of subarachnoid space	?	+	+	+	+	+	+	+	+	+	9/9
Deformation/compression of cervical spinal cord	?	+	+	+	+	+	+	+	+	+	9/9

[a] In comparison with achondroplasia standards (Todorov et al. 1981).
[b] Reflects parental/caregiver concern, without objective documentation.
[c] "Prickling" in arms and neck with neck flexion; irritation and stroking and "picking" at right buttock.
[d] See example 2 in text.
[e] See example 1 in text.
[f] Hypersomnia (sleeping >16 h in each 24-h period) just prior to decompression.
[g] Weak cry; failure to thrive.
[h] Progressive neck hyperextension when orthograde and unwillingness to flex neck prior to decompression.
[i] Recurrent unexplained irritability.
[j] See example 4 in text.
[k] See example 3 in text.
[l] Left vocal cord paralysis confirmed by bronchoscopy.
[m] Disporportionate to that expected in infants with achondroplasia.
[n] Marked neck hyperextension, with occiput resting between scapulae.
[o] Preference for neck hyperextension.
[p] Little spontaneous activity.

cause of already recognized neurological dysfunction and in whom decompression occurred later in life, often were left with significant residual disability (see Example 4, below). There were no significant intraoperative complications. In one case there was a transient postoperative cerebral spinal fluid leak; there were no other postoperative complications. None suffered permanent sequelae attributable to the surgery.

Exemplary Cases

Described are two examples of prospectively ascertained infants who underwent decompressive surgery (examples 1 and 2), two retrospectively assessed infants whose histories illustrate the variety of features with which children with cervicomedullary compression may present (examples 3 and 4), and, finally, the one child within the prospective

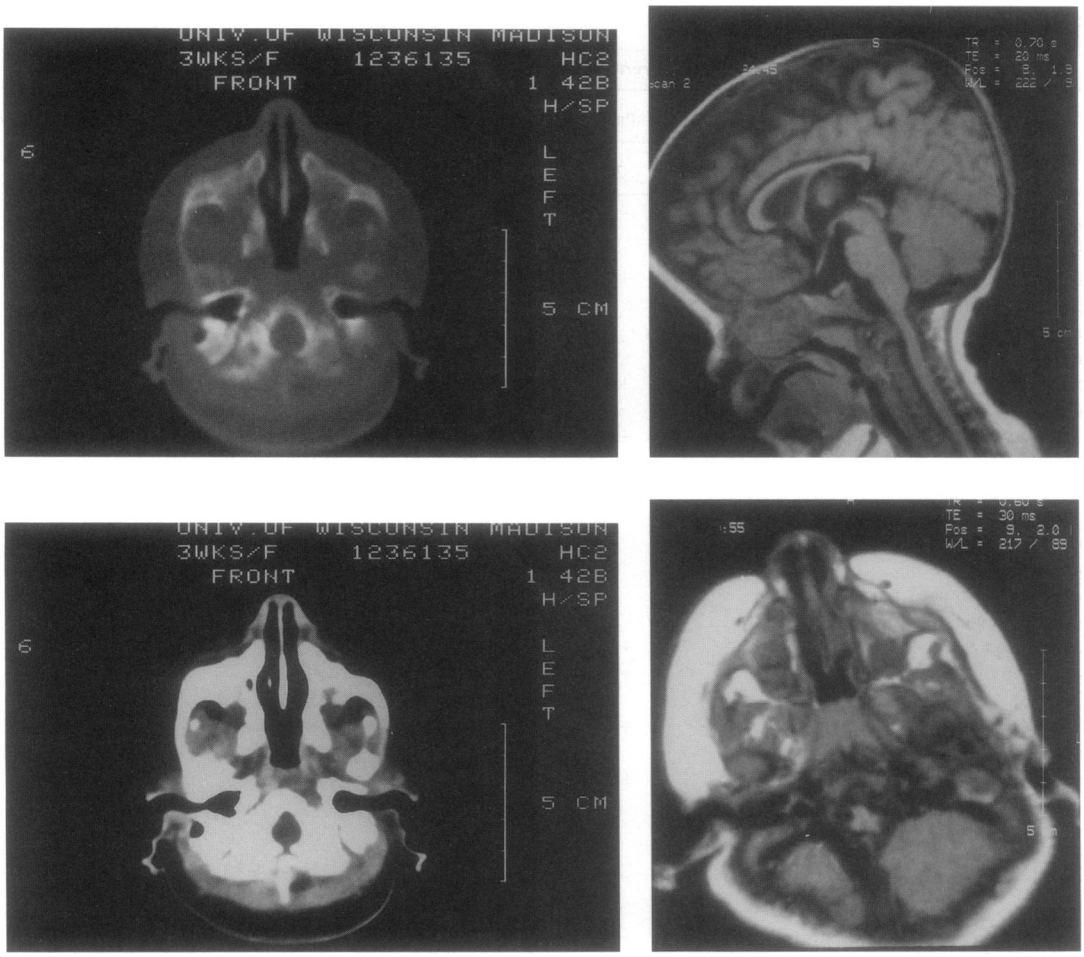

Figure 1 Computed tomography (*left*, with bone windows shown in the lower panel) and magnetic resonance imaging (*right*) of the foramen magnum of example 1, demonstrating constriction of the foramen and deformation of the upper cervical cord as described in the text.

group who died during the period of care summarized here (example 5).

Example 1.—This female was born by cesarean section at 37.7 wk gestation, because of increasing maternal dyspnea and developing respiratory failure related to the mother's achondroplasia. Achondroplasia was recognized by prenatal ultrasound and was confirmed by examination shortly after birth. Birth measurements were normal. The newborn period was uneventful. Parents observed possible asymmetric leg movement (right leg moved more than left) by ~3 wk of age, but examination at that time only demonstrated moderately decreased truncal and limb tone and isolated unsustained clonus of the right ankle. Computed tomography at 1 mo of age showed foramen magnum measures below the mean for achondroplasia (fig. 1) (Hecht et al. 1989). Multichannel sleep study demonstrated central hypopneas with minimal oxygen saturation of 83%. By age 7 mo the patient had gross motor delays beyond those expected for a child with achondroplasia (Todorov et al. 1981), had not developed head control, had poor trunk tone, and had unexplained recurrent emesis. There was minimal asymmetry of voluntary leg movement and persistence of the right ankle clonus seen earlier. Occasional arching and hyperextension of the trunk was observed. There was strong clinical suspicion that craniocervical junction compression was present. Magnetic resonance imaging revealed severe distortion of the upper cervical cord at the level of the foramen magnum, resulting in a cervical cord reminiscent of a four-pointed star (fig. 1). Given these findings and the persisting abnormalities of neurological examination, the patient underwent suboccipital decompressive surgery at age 8 mo. Intraoperative findings included marked compression of the cord at the level of the foramen magnum. Recovery was uneventful. Hypotonia and gross motor function improved, with completely normal findings by developmental and neurological assessment by age 2 years. She is now cognitively and neurologically normal at 5 years of age.

Example 2.—This female was born by repeat cesarean section at 39 wk gestation, after late-gestation ultrasound suggested that the fetus was affected with either achondroplasia or hypochondroplasia. Achondroplasia was diagnosed clinically and radiologically shortly after birth. Neonatal problems included transient tachypnea and oxygen

dependence and several episodes of apnea and cyanosis. Home monitoring was initiated at discharge. A severe apneic episode at home occurred at age 19 d. Despite these events she was referred to us at 1½ mo of age, as an achondroplastic infant without special problems. By history, she had breathing difficulties associated with feeding and episodic tachypnea. Examination showed no neurological abnormalities except for bilateral ankle clonus (an equivocal finding, given the patient's age), as well as frequent glottal stops, tracheal tug, tachypnea, and marked paradoxical chest movement. Overnight polysomnography demonstrated central hypopneic episodes with minimum oxygen saturations of 83%; multiple short (<10-s) respiratory pauses were recorded. Computed tomography revealed a foramen magnum with a transverse diameter below the mean and with longitudinal dimension above the mean, compared with achondroplasia standards (Hecht et al. 1989). By age 7 mo, respiratory concerns had increased: the patient's mother reported persistent tachypnea, periodic grunting and glottal stops, and respiratory pauses. In addition, neurological assessment now demonstrated little improvement of truncal tone and persistent bilateral ankle clonus. Shortly thereafter, her mother noted decreasing head control, spontaneous ankle clonus, and onset of unusual breathing described as a series of rapid inspirations without intervening expiration that were followed by an inspiratory pause, with such patterns usually persisting for 10–15 min both when she was awake and when she was asleep; this description seemed consistent with a variant of apneustic breathing (Mador and Tobin 1990). Magnetic resonance imaging showed a constricted foramen magnum with complete obliteration of the subarachnoid space surrounding the upper cord, as well as moderate posterior and anterolateral deformation of the cord itself. Suboccipital decompression was carried out at 9 mo of age. Marked cord deformation was confirmed intraoperatively. She had rapid resolution of hypotonia and ankle clonus and marked decrease in the frequency of apneustic breathing. Now, at age 18 mo, her development, including gross motor skills, has normalized, and, while concerns have now arisen about development of obstructive sleep apnea, episodes of apneustic-like breathing have remained infrequent.

Example 3.—This male was born by vaginal delivery following an uncomplicated pregnancy. Achondroplasia was recognized neonatally. He was first seen by us at age 19 mo. He had marked motor and personal/social delays by screening, had slowing of weight gain, and, by report, had preferential use of his right hand and arm. There was no history suggestive of disruption of central respiratory control. Previous serial ultrasonography had demonstrated stable, mild ventriculomegaly and extra-axial fluid typical for infants with achondroplasia. Computed tomography had been completed at age 17 mo and showed the longitudinal foramen magnum size to be below the mean for achondroplasia (Hecht et al. 1989). Examinations at 19 and 22 mo of age showed severe thoracolumbar kyphosis, markedly decreased truncal and moderately decreased extremity tone, decreased resistance in all limbs, and right-hand preference for manipulation of objects, but no other objective evidence of asymmetries. On the basis of his persistent, severe hypotonia and marked motor delays, the possibility of cervical cord compression was considered. Magnetic resonance imaging at 22 mo showed obliteration of the subarachnoid space at the craniocervical junction and considerable deformity of the upper cervical spinal cord. Additional neuroimaging with metrizamide contrast confirmed deformation of the cord, and suboccipital decompression was completed at 23 mo of age. Reassessment at 27 mo of age showed dramatic improvement of truncal tone, acceleration of gross motor development, and modest improvement of weight gain.

Example 4.—This female was first assessed in our clinic at 29 mo of age. Although she had shown somewhat greater than average delays in motor development, no other problems had arisen prior to 23 mo of age. At that time her parents noted that she began to crawl less and to pull to stand less than previously. By 26 mo of age her parents had observed dragging of the left leg, and by 27 mo she could no longer independently hold a cup; she had progressive decreased use of her left arm and hand. By the time she was referred, she had lost her ability to stand or cruise with support and to sit independently. Neurological assessment showed marked hypotonia and marked asymmetries of tone and resistance (much less in the left arm and left leg). There was bilateral hyperreflexia and clonus in the legs (worse in the left leg), while the left arm was areflexic. Computed tomography showed foramen magnum measurements that were average for age and diagnosis. Somatosensory evoked–potential testing showed ablation of wave forms above C_2. Emergent decompressive surgery was carried out, during which the upper cervical cord was noted to be profoundly compressed and ribbonlike. Considerable improvement occurred postoperatively, so that within 3 mo all skills that had been lost were regained. Both asymmetric generalized left-sided weakness and hyperreflexia of the left leg persisted. With continued therapy she learned to walk independently by 9 years of age, and currently, at 12 years of age, she continues to make slow progress, although she remains motorically handicapped. Her most recent assessment demonstrates selective weakness of the left shoulder girdle, biceps, and wrist extensors; weakness of the left hip flexors and ankle dorsiflexors; hyperreflexia and clonus of the left leg; upgoing response to Babinski stimulation on the left side; decreased light-touch and pinprick sensation of the lateral margin of the right foot; and inability to distinguish hot and cold in the right lower leg. She is cognitively normal.

Example 5.—This male was delivered vaginally following a 39-wk gestation and a 24-h labor requiring Pitocin augmentation. Diagnosis of achondroplasia was made in in-

fancy. There were no neonatal problems. He was first evaluated in our center at 7 mo of age, at which time there were modest neurological concerns both historically and by examination: poor neck and trunk tone, left-hand preference, and tendency to hyperextend his neck and rest his occiput on his shoulders. Computed tomography showed foramen magnum measures near the means for infants of his age who have achondroplasia. Overnight polysomnography showed frequent central hypopneic episodes with desaturations into the 80%–85% range. On reassessment at age 10 mo, tone was still thought to be outside the normal range for children with achondroplasia. Although recommended at this time, neither repeat sleep study nor magnetic resonance imaging was completed secondary to parental preference. He did show gradual improvement of truncal tone and overall strength at 10–20 mo of age, although he never caught up with anticipated gross motor norms for his diagnosis. At 20 mo, examination also showed marked jugular venous distension with crying; cardiologic assessment was not revealing, and it was suggested that the jugular venous distension could be related to restriction of thoracic flow secondary to diminished chest size. He was last seen at age 31 mo, at which time no new features were elicited by history or examination. His examination remained worrisome only because of continued persistence of truncal hypotonia and decreased neck and trunk strength. He died unexpectedly while asleep, at 32 mo of age. Postmortem assessment (done elsewhere) documented cystic degenerative changes of the lower brainstem and syrinx of the upper cervical cord; his death was attributed to respiratory arrest secondary to chronic brainstem compression. No antecedent trauma was documented.

Characteristics of the Prospectively Assessed Population

Within the prospectively assessed group, mean age at first assessment was 4.5 mo (range 0.4–12.0 mo). Potentially relevant variables are shown in tables 3 and 4, in which, for characteristics that are not continuous, semiquantitative scales are used to clinically estimate the severity of the feature.

Head-circumference data (table 3) generally correspond to the distributions previously published (Horton et al. 1977). Seven individuals had acceleration of head growth during the first year of life (table 3), but only three of these underwent ventriculoperitoneal shunting, whereas in the others the rate of head growth normalized. It is conceivable that transient increases in intracranial pressure account for this latter group. About a third of all infants had prominence of superficial venous patterning over the calvarium and/or face (table 3), which might be secondary to modification of emissary venous flow secondary to jugular foraminal constriction (Mueller and Reinertson 1980; Pierre-Kahn et al. 1980; Yamada et al. 1981). Neurological evaluations were, when compared with those for average children, virtually always abnormal. The frequency of decreased trunk tone, decreased limb tone, and decreased resistance and strength in the legs are so frequent (table 3) as to be normative for the achondroplasia population. In contrast, the infrequency with which asymmetries and hyperreflexia are noted (table 3) suggests that these findings should be viewed with greater concern. In assessing predictors of need for decompression, only moderate or greater decreases in tone and strength were considered abnormal for this population, whereas any asymmetries or hyperreflexia were assumed to be pathologic. Nearly half of evaluated children also had abnormal neurological histories (table 3), with asymmetries, weakness, hypotonia, and back arching or opisthotonic episodes being most frequently reported.

Computed tomography (table 4) showed ventriculomegaly in three-fourths of those assessed. In addition, a similar number had considerable extra-axial fluid accumulation (which, in this population, should not be confused with cortical atrophy). Distribution of the measured size of the foramen magnum transverse diameter corresponded to that previously published (Hecht et al. 1989), but almost three-fourths of the longitudinal diameter measures exceeded the age-specific mean (Hecht et al. 1989). The source of the latter discrepancy is unknown.

Magnetic resonance imaging was completed on 21 of the prospectively assessed infants (table 4). Because it was used selectively, often related to other clinical and neurological concerns, the distribution of craniocervical junction features does not necessarily reflect the characteristics of the entire population. Given that caveat, most studies nonetheless showed abnormality of the craniocervical junction. Many infants with narrowing or obliteration of the subarachnoid space or subtle "nicking" of the posterior cord were and remain neurologically normal. Such features, therefore, should never be used by themselves to decide whether an infant is in need of craniocervical decompression.

Central apnea and, more often, central hypopnea were frequently demonstrated through overnight polysomnography (table 4). The latter is characteristic of achondroplasia and will be reported in more detail separately.

Antecedent Prediction of Need for Suboccipital Decompression

To assess which investigations are of greatest predictive value in identifying the subset of children who have unequivocal compression in need of intervention (and who, by implication, would have a much higher risk of death without such intervention), we have chosen to use the fact of them having undergone suboccipital decompressive surgery as a placeholder for the life-threatening events themselves. This apparent tautology is explored in the Discussion. Five of 53 infants with achondroplasia ascertained prospectively ultimately underwent suboccipital decompression. Possible predictive variables of the need for suboccipital decompression are shown in table 5. Correlation coefficients for each of the variables identified as signifi-

Table 3

Clinical Variables within the Prospectively Ascertained Population (*N* = 53)

	<5 Percentile	6–24 Percentile	25–49 Percentile	50–74 Percentile	75–94 Percentile	>95 Percentile
Craniofacial features:						
Head size	3 (5.7%)	4 (7.5%)	19 (35.8%)	24 (45.3%)	3 (5.7%)	0
		Yes			No	
Acceleration of head growth in 1st year		7 (13.5%)			45 (86.5%)	
Bulging/tense frontanel		1 (2.0%)			48 (98.0%)	
	Normal/Minimal		Mild	Moderate		Marked
Calvarial superficial venous prominence	28 (68.3%)		11 (26.8%)	1 (2.4%)		1 (2.4%)
Craniofacial disproportion	2 (4.9%)		23 (56.1%)	15 (36.6%)		1 (2.4%)
Parietal bossing	4 (10.8%)		19 (51.4%)	12 (32.4%)		2 (5.4%)
Frontal bossing	7 (16.3%)		23 (53.5%)	11 (25.6%)		2 (4.7%)
Midfacial hypoplasia	5 (12.5%)		19 (47.5%)	13 (32.5%)		3 (7.5%)
Neurological examination:						
Cranial nerve abnormality	48 (100.0%)		0	0		0
Decreased truncal tone	11 (28.2%)		22 (45.4%)	6 (15.4%)		0
Decreased limb tone	13 (29.5%)		23 (52.2%)	8 (18.2%)		0
Arm resistance/strength	27 (67.5%)		12 (30.0%)	1 (2.5%)		0
Leg resistance/strength	20 (50.0%)		17 (42.5%)	3 (7.5%)		0
		Yes			No	
Asymmetries of resistance/strength		3 (6.2%)			45 (93.8%)	
Hyperreflexia in arms		0			48 (100.0%)	
Hyperreflexia in legs		9 (19.1%)			38 (80.9%)	
Asymmetric reflexes		3 (6.5%)			43 (93.5%)	
Ankle clonus		9 (19.1%)			38 (80.9%)	
Neurological history:						
Disproportionate developmental delays		5 (9.6%)			47 (90.4%)	
Observed asymmetries		11 (21.2%)			41 (78.8%)	
Observed weakness/hypotonia		7 (13.5%)			45 (86.5%)	
Observed sensory abnormalities		2 (3.8%)			50 (96.2%)	
Observed arching/opisthotonos		5 (9.6%)			47 (90.4%)	
Observed clonus		4 (7.7%)			48 (92.3%)	
Seizures		4 (7.7%)			48 (92.3%)	
Observed apnea		14 (26.9%)			38 (73.1%)	
Any abnormality by neurological history		22 (42.3%)			30 (57.7%)	

NOTE.—All of the percentages exclude missing data. While in most instances such missing information likely reflects absence of the feature, if that characteristic was not explicitly documented in the clinic notes, then it was excluded for that case.

cantly associated with need for decompression were, individually, modest (table 5). From the 12 items identified in table 5 as being significantly associated with surgery, we attempted to select a set of variables that plausibly could be considered independent of one another and that would likely be readily replicable from observer to observer. Four variables that appear to meet these criteria—both foramen magnum measures below the mean for achondroplasia, hyperreflexia/clonus on examination, decreased limb tone, and central hypopnea—were used for exploratory logistic regression analysis. Decreased limb tone did not appear to be an important predictor (β weight = -0.457) and was eliminated. The other three variables resulted in 96.7% correct prediction (one misclassification) by logistic regression analysis (model $\chi^2 = 19.74$; $P = .0002$); each variable appeared to contribute equally to the model (for foramen magnum measures, hyperreflexia, and hypopnea, β weights were 11.80, 12.95, and 11.65, respectively). Finally, for these three variables alone and in combination, sensitivity, specificity, accuracy, and predictive powers were calculated (table 6).

Genotype and Need for Decompression

In 49 of these infants, molecular studies have been completed, and 45 have shown the presence of the common mutation in FGFR 3 (Shiang et al. 1994). Five of the 45

Table 4

Laboratory Variables within the Prospectively Ascertained Population (*N* = 53)

	Normal/Minimal	Mild	Moderate	Marked
Computer tomography:				
Ventriculomegaly[a]	8 (22.2%)	7 (19.4%)	17 (47.2%)	4 (11.1%)
Extra-axial fluid[a]	8 (25.8%)	14 (45.2%)	4 (12.9%)	5 (16.1%)
	>1 SD above mean	0 to +1 SD	0 to −1 SD	>1 SD below mean
Foramen magnum longitudinal diameter	3 (7.5%)	26 (65.0%)	9 (22.5%)	2 (5.0%)
Foramen magnum transverse diameter	7 (17.5%)	15 (37.5%)	14 (35.0%)	4 (10.0%)

	Normal	Narrowing of Subarachnoid Space	Obliteration of Subarachnoid Space	Nicking of Cord	Cord Deformation
Magnetic resonance imaging of craniocervical junction[b]	6 (28.6%)	15 (71.4%)	11 (52.4%)	9 (42.8%)	5 (23.8%)

	None	Mild	Moderate	Severe
Polysomnography:				
Central apnea	21 (60.0%)	11 (31.4%)	2 (5.7%)	1 (2.9%)
Central hypopnea	12 (34.3%)	7 (20.0%)	6 (17.1%)	10 (28.6%)
Obstructive apnea	27 (77.1%)	8 (22.9%)	0	0

NOTE.—Missing data include those which were not recorded or which could not be retrieved.

[a] Any who had ventriculoperitoneal shunting prior to the reviewed studies are also excluded from these enumerations.

[b] Entries in 2d–5th columns are cumulative totals.

with the common mutation underwent suboccipital decompression, whereas none of the 4 in whom this mutation was not detected has been surgically decompressed.

Discussion

Achondroplasia is the most common skeletal dysplasia. Although short stature is the most obvious result, affected individuals are at risk for a large number of medical complications as well, most of which are consequences of disproportion between endochondral bones and other tissues and organs.

A persisting frustration of providing clinical care to individuals affected by many genetic disorders is the lack of natural history studies. Too often we must depend on anecdotal data based on the summed information available in case reports, despite the ascertainment and publication biases of such sources. This report provides data concerning the neurological course of infants with achondroplasia who were ascertained prospectively and without specific medical indications for referral.

Historical, clinical, and laboratory abnormalities referable to the upper cervical cord are common in infants with achondroplasia (tables 3 and 4). Certain of those features appear to be predictive of the need for suboccipital decompressive surgery (table 5). Surgical intervention is effective in modifying the course of cervical cord compression, and, without careful assessment and timely surgical intervention, some infants with achondroplasia will die or be left with permanent neurological sequelae.

Risks for and Consequences of Cervicomedullary Compression in Achondroplasia

Risks for myelopathic sequelae of upper-cervical cord damage in both infants and children with achondroplasia have been demonstrated elsewhere (Yang et al. 1977; Yamada et al. 1981; Blondeau et al. 1983; Colamaria et al. 1991). Other reports had suggested a relationship between craniocervical junction abnormalities and respiratory deaths in infancy (Yang et al. 1977; Yamada et al. 1981; Bland and Emery 1982; Stokes et al. 1983), and a decade ago we documented that compression of the brainstem and upper cervical cord can result in sudden, unexpected death in infants with achondroplasia (Pauli et al. 1984). Compression probably arises because of asynchronous growth of the endochondral bone–derived basicranium (Spranger 1988) compared with neural elements, the virtually uniform hypotonia seen in babies with achondroplasia, and their macrocephaly, which, together, increase the likelihood of uncontrolled head movement around a smaller than normal foramen magnum. Death from central apnea likely results from damage to the respiratory control centers of the inferior medulla, either directly or from ischemic damage secondary to compression of the vascular supply to the medulla (Pauli et al. 1992). Similar mechanisms probably

Table 5

Variables Compared, between Group of Prospectively Ascertained Infants Who Underwent Suboccipital Decompression and Those Who Did Not

Feature	No. (%) Positive			Significance[a]	Correlation[b]
	Decompressed (n = 5)	Not Decompressed (n = 48)			
Craniofacial features:					
Acceleration of head growth	3/5	4/47	8.5		
Calvarial venous prominence[c]	1/5	1/36	2.8		
Craniofacial disproportion[c]	5/5	11/36	30.6	.006	.31
Parietal and/or frontal bossing[c]	5/5	14/32	43.8	.03	.26
Midfacial hypoplasia[c]	4/5	12/35	34.3		
Any craniofacial abnormality	5/5	22/34	64.7		
Neurological examination:					
Decreased truncal tone[c]	1/5	5/34	14.7		
Decreased limb tone[c]	3/5	5/39	12.8	.03	.32
Decreased or asymmetric arm strength/resistance	0/5	1/40	2.5		
Decreased or asymmetric leg strength/resistance	1/5	2/40	5.0		
Hyperreflexia/clonus in legs	4/5	5/42	11.9	.003	.42
Asymmetric reflexes	1/5	2/41	4.9		
Any abnormality by neurologic examination	5/5	8/32	25.0	.003	.38
Neurological history:					
Disproportionate developmental delay	2/5	3/47	6.4		
Sensory abnormalities	0/5	2/47	4.3		
Asymmetries	3/5	8/47	17.0		
Weakness/hypotonia	2/5	5/47	10.6		
Arching/oposthotonos	1/5	4/47	8.5		
Observed clonus	2/5	2/47	4.2	.04	.44
Seizures	1/5	2/47	4.2		
Any abnormality by neurological history	5/5	12/47	25.5	.002	.29
Computed tomography:					
General:					
Marked ventriculomegaly	0/5	4/33	12.1		
Marked extra-axial fluid	1/5	4/29	13.8		
Foramen magnum:					
Longitudinal diameter less than the mean	3/5	8/35	22.9		
Transverse diameter less than the mean	5/5	13/35	37.1	.01	.28
Both diameters less than the mean	3/5	4/35	11.4	.03	.37
Either diameter less than the mean	5/5	17/35	48.6	.04	.23
Longitudinal diameter <−1 SD	1/5	1/35	2.9		
Transverse diameter <−1 SD	2/5	2/35	5.7		
Both diameters <−1 SD	0/5	0/35	0		
Either diameter <−1 SD	3/5	3/35	8.6	.02	.44
Polysomnography:					
Central apnea[d]	0/5	3/30	10.0		
Central hypopnea[e]	4/4	12/30	40.0	.04	.25

NOTE.—Only those with unequivocal documentation on *initial* examination are counted, hence the variable denominators; that the features had to be documented on *initial* examination results in some differences when tables 3 and 4 are compared with the data presented here.

[a] Shown are those in which there was a significant difference by Fisher's exact test (one-tail).

[b] Asymmetric Somer's D with decompression as the dependent variable.

[c] Abnormal = moderate/marked.

[d] Apneic episodes >10-s duration and/or >100 central pauses of <10-s duration during a single overnight study.

[e] Evidence for abnormality of central respiratory control, including hypopneic episodes with desaturations ≤85% and/or end-tidal carbon dioxide levels >50 mmHg.

cause the cervical myelopathic changes in other infants with achondroplasia.

Since virtually all children with achondroplasia share the main risk features, some nonspecific recommendations regarding care of all infants with achondroplasia seem appropriate, including careful neck support with handling, use of a "baby safe," use of a rear-facing car seat, and proscription of use of motorized swings (see Pauli et al.

Table 6

Sensitivity, Specificity, Accuracy, and Predictive Powers of the Selected Variables, Alone and in Combination, Associated with Ultimate Need for Suboccipital Decompression

Variable	Sensitivity	Specificity	Accuracy	Predictive Power	
				Positive	Negative
Hyperreflexia/clonus in legs	.80	.88	.87	.44	.97
Computed tomography of foramen magnum: both diameters less than the mean	.75	.89	.87	.43	.97
Central hypopnea	1.00	.60	.65	.25	1.00
Any one of three abnormal	1.00	.60	.64	.22	1.00
Any two of three abnormal	.80	.97	.95	.80	.97
All three abnormal	.50	1.00	.93	1.00	.93

1984), doorway jumpers, "snugglies," and umbrella strollers, all of which may increase the likelihood of disadvantageous head position and/or uncontrolled head movement. Vigorous suctioning may also be contraindicated (Pauli et al. 1984), perhaps on the basis of reflex cardiac arrest, as described by Frankel et al. (1975), in individuals with high cord transections. Vaginal delivery (Bland and Emery 1982) does not appear to be a risk factor.

In individuals with achondroplasia, Hecht et al. (1987) found excess mortality of ~7.5% in the first year of life and of ~2.5% at 1–4 four years of age. Most deaths were sudden and unexpected, and, of those autopsied, most showed evidence for upper cervical cord compression. Thus, 1 in 10–15 infants with achondroplasia may die from this complication, although some clinicians have suggested that the real risk may be much less (Wassman and Rimoin 1988). Among the 75 infants assessed by us, 2 (2.7%) deaths have occurred. Ten other infants and children (13.3%) have had surgery because of clinical indicators of risks related to craniocervical compression. Among the 53 infants prospectively ascertained, 2 died and 5 more (9.4%) underwent decompression. Since there is no proof that death was avoided by surgery, no unequivocal estimate of risk for death in an untreated population can be made. Nonetheless, these data do suggest that risk for life-threatening consequences is substantial.

Reid et al. (1987) and Francomano et al. (1993) have presented similar data. Although highly selective secondary to referral bias and thus providing no comparable estimates of the frequency of features relevant to possible cord compression for the general population of infants with achondroplasia, these studies confirm (1) the frequent occurrence of neurological and respiratory complications in infants with achondroplasia and (2) the utility of comprehensive assessment.

Clinical Presentation in Infants Judged to Need Suboccipital Decompressive Surgery

In no instance was decompression carried out solely on the basis of neuroimaging or electrophysiologic abnormalities, since some individuals who appeared to be neurologically intact nevertheless displayed abnormalities by such testing. Infants who underwent decompressive surgery had multiple clinical features of cervical myelopathy, including hypotonia, weakness, asymmetries, and hyperreflexia (table 2). Most healthy infants with achondroplasia are neurologically abnormal when compared with an unaffected population, particularly in being hypotonic; however, *persisting* hypotonia, weakness, and/or developmental delays are important clues to possible craniocervical risks. In contrast, asymmetries are not frequent in infants with achondroplasia and always should precipitate further investigation. We frequently documented hypopneas–but (in contrast to the reports by Reid et al. [1987] and Francomano et al. [1993]) not central apnea—by polysomnography (table 4). Both seizures (Bland and Emery 1982; Colamaria et al. 1991; Yang et al. 1977) and apneustic breathing (Mador and Tobin 1990) also have been reported previously in infants with achondroplasia and cervical cord abnormalities. Infants who eventually underwent decompressive surgery often showed neck hyperextension so marked that they would rest the head between the scapulae. Since such hyperextension should exacerbate cord compression (Yang et al. 1977), there seems to be no biophysical explanation for this characteristic.

Utility of Surgical Intervention

All 10 infants who had surgery showed marked clinical improvement. Those with residual neurological sequelae were from the nonprospective population and had suffered irreversible damage prior to referral. Decompressive surgical intervention is of clear benefit to infants and children with achondroplasia and evidence for cervical myelopathy (Yamada et al. 1981; Reid et al. 1987; Wang et al. 1987; Carson et al. 1988; Francomano et al. 1993). Delays in intervening can result in irreversible consequences (Pierre-Kahn et al. 1980; Hecht et al. 1984; Colamaria et al. 1991). It is less certain whether timely surgical intervention prevents apnea-precipitated deaths.

In our population, the only postoperative complication

was a cerebrospinal fluid leak (Carson et al. 1988). However, this surgery is not without risk (Reid et al. 1987; Francomano et al. 1993), and decisions to subject an infant to such a procedure must be made with caution. Nonetheless, deaths secondary to cord compression certainly do occur (Pauli et al. 1984; Hecht et al. 1987; example 5 in this report), and cord compression is not simply a normal concomitant of achondroplasia (Wassman and Rimoin 1988). Therefore, accurately identifying those in need of surgery is crucial.

Risk Factors That May Help Anticipate Need for Suboccipital Decompressive Surgery

Information available when these evaluations began (Yang et al. 1977; Bland and Emery 1982; Blondeau et al. 1983; Fremion et al. 1984; Pauli et al. 1984) precluded any limitation of or randomization for intervention. To assess which studies may identify the subset of children who have unequivocal compression, we defined that subset on the basis of their subsequently having undergone surgery. On the surface this may appear tautological—defining as in need of surgery those who eventually undergo the procedure. However, we think that this is a true tautology only if surgical intervention sometimes fails to confirm the presence of cord compression (which has never been observed either in the present report or in other published reports), *or* if one posits that surgically confirmed cervical spinal cord compression is not always pathological (biologically implausible and never before described under any circumstance), *or* one posits that many infants not undergoing decompressive surgery have severe anatomic cord compression that remains asymptomatic and unrecognized (formally possible but, in our opinion, unlikely).

Within those limitations, surgery can be used as an endpoint indicative of a case being in a high-risk group. Twelve variables were identified as having potential utility in identifying those needing surgical intervention (table 5). They include at least one in each of the major categories of evaluation: craniofacial examination, neurological examination, neurological history, computed tomography, and polysomnography. A conservative recommendation would be to include all of these components in assessment of every infant with achondroplasia. Three variables—hyperreflexia or clonus, foramen magnum measures below diagnosis-specific means, and central hypopnea—in combination result in 97% accuracy of prediction by logistic regression. While not suggesting that only these three variables be assessed, we believe that special attention should be paid to any infant who has abnormalities of all of these three features.

Conclusions and Recommendations

Infants with achondroplasia are at risk for cervical cord–associated complications, including death. Selective intervention can be life and health saving. High-risk infants can be identified through comprehensive evaluation, which should be completed as soon as the diagnosis is confirmed and which should include careful neurological history, neurological and general examination, computed tomography including thin cuts of the foramen magnum, and polysomnographic evaluation. Our current practice includes such evaluation of all infants at the time of first referral. In those with reassuring findings, follow-up includes only careful neurological and respiratory histories and clinical and neurological reassessments approximately every 6 mo. No additional neuroimaging or other evaluations are undertaken unless new historical or clinical features arise. In those with demonstrable risk factors, magnetic resonance imaging is performed. If compression is clearly demonstrated in the presence of other abnormal findings, then surgery is recommended. If no unequivocal evidence for compression is found by magnetic resonance imaging, then, in these presumably high-risk children, clinical reassessment and neuroimaging are repeated at ~4-mo intervals until the children are 2 years of age. No additional neuroimaging of older children is undertaken except when indicated by new clinical features.

Cervical cord and brainstem compression is probably a mechanism of death and disability in various bone dysplasias (as one might anticipate, given the commonality of disproportionate bone and soft-tissue growth in these disorders). Anecdotal evidence suggests this as a mechanism of death not only in heterozygous achondroplasia but also in homozygous achondroplasia (Yang et al. 1977; Pauli et al. 1983; Hecht et al. 1986; Moscowitz et al. 1989), thanatophoric dysplasia (Ho et al. 1984), campomelic dysplasia (authors' personal observation), and osteogenesis imperfecta type II (Pauli and Gilbert 1986).

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